REMARKS

Claims 1 - 14 have been cancelled, rendering any rejections thereof moot. Claims 15 – 27 are pending. Claim 22 has been amended to correct a minor clerical error, placing the claim in proper independent form. Claim 24 is amended to correct the spelling of hydrazone.

This amendment does not affect the scope of the claim. No new matter is added by this amendment.

I. Specification

The specification has been corrected to reflect the patent number of the parent application and the status of the grandparent application. This correction overcomes the objection to the specification.

II. 35 USC 103

Claims 1 - 27 have been rejected under 35 USC 103 as being unpatentable over Morris et al, US Patent 5,516,781 or Mitchell et al, US Patent 5,288,711, in view of Wright et al, US 6,585,764, Schuler et al, US 6,384,064, Somers et al, US 6,121,319, Applicants' statement on page 5, line 10 – page 6, line 22 of the specification, and "The Merck Manual of Diagnosis and Therapy".

Applicants respectfully traverse this rejection.

In summary, there is no motivation in the art to combine the teachings of the document. In fact, the teachings of Mitchell (which requires a component not recited in the claims) and Somers (which contains no teaching of a rapamycin) would lead one of skill in the art away from such a combination and any expectation of success. However, even if combined, the cited combination fails to suggest the present invention.

The documents cited by the examiner which teach the use of a rapamycin, *i.e.*, Morris, Mitchell, Schuler, and Wright, teach treatment of cellular proliferation (treatment of disorders associated with a hyperproliferative condition), which in some situations is induced by a preexisting injury to a vascular cell wall. The combined

teachings of these documents do not suggest that rapamycin could be useful in prevention or inhibition of lipid accumulation or disorders caused by lipid accumulation even in the absence of a preexisting hyperproliferative condition.

The following discussion addresses the three points raised on page 5 of the Office Action by the examiner:

(i) *The examiner argues that one of skill in the art concerned with hyperproliferative vascular disease would have been aware of not only Morris or Mitchell, but of Schuler as well, which is relied upon for teaching treatment of hyperproliferative vascular diseases including atherosclerosis with rapamycin derivatives.*

The description to the treatment using rapamycin in Morris, Mitchell, Wright and Schuler, are based on the anti-hyperproliferative effect of rapamycin following direct injury to the cell wall, but none of the cited documents assessed the ability of the compounds to prevent lipid deposition or accumulation by the direct effect on plasma lipids.

The accumulation of lipids in the walls of blood vessels is an important aspect of the atherosclerotic process, but the prior art does not teach or suggest the use of a rapamycin for the prevention of lipid deposition or accumulation in a vascular wall, or the treatment or prevention of conditions that are associated with such lipid deposition or accumulation.

The data in the present application demonstrates the effect of rapamycin on plasma lipids and supports the medical use as expressed in claim 1. Low levels of HDL are considered a risk factor for vascular disease; similarly, elevated triglyceride levels are considered a risk factor. Table 1 in the present application shows that treatment with rapamycin significantly increased levels of HDL cholesterol, while not significantly affecting levels of triglycerides. The Table also goes on to shows there is a dramatic three fold reduction in the level of aortic atherosclerosis. As the description points out the aortic atherosclerosis data is a well accepted model of human atherosclerosis.

Thus, in the present situation the prior art is concerned with the effect of a rapamycin on hyperproliferation following vascular cell damage caused by

injury, whereas the experiments described in the present specification by the Applicants are concerned with the plasma lipid/triglyceride levels and aortic atherosclerosis of normal animals.

(ii) It is noted that Somers contains no teaching related to a rapamycin. Nor does Somers provide any suggestion to combine any other pharmaceutical agents with a rapamycin.

Somers teaches a method of treatment utilizing monoesters of probucol, optionally in combination with other medications. This document does not teach or suggest the use of a rapamycin. Thus, the combined teaching in this document with the other cited documents does not supply the missing suggestion necessary to render the present invention obvious.

(iii) The examiner notes that Morris teaches that rapamycin can treat hyperproliferative vascular diseases, including atherosclerosis. The examiner further notes that Morris describes atherosclerotic lesions as including lipid laden "foam cells".

Applicants respectfully draw the examiner's attention to the fact that the same passage in Morris attributes this to restenosis produced by proliferation of cells following a breech of endothelial cell wall integrity.

Neither Morris nor Mitchell suggest the use of any rapamycin derivatives, much less the derivatives recited in the present invention. The combination of the secondary references with Morris or Mitchell fails to suggest the present invention. Further, Mitchell teaches away from the present invention, as it requires the presence of heparin, which is not an element of the claimed invention.

Similarly, the teaching of Wright, which relates to localized delivery of rapamycin, are focused on addressing restenosis following injury to vascular wall injury.

As previously noted, Mitchell requires the presence of an element not recited in the present application and thus, teaches away from the present invention. Further, three of the secondary references, *i.e.*, Somers, Merck and Wright do not even discuss the use of a rapamycin.

However, even if the teachings of the *six* documents relied upon are combined, their teachings are disparate and fail to supply the suggestion necessary to render the present invention obvious.

The examiner relies upon Merck for its general teachings relating to stroke or multiinfarct dementia.

Applicants respectfully submit that Merck fails to supply the suggestion missing from the combined teachings of the other documents.

In many cases, vascular cell damage can be caused by lipid accumulation. However, if lipid accumulation can be prevented, vascular cell damage and the formation of plaques can also be prevented. The prevention of the formation of these plaques is useful for prevention and treatment of disorders including stroke and multiinfarct dementia.

Thus, while the ability of a rapamycin to treat cellular hyperproliferation was described in certain of the references, prior to the present invention, the ability of rapamycin to prevent lipid accumulation was previously unrecognized. The combined teachings of the cited documents fail to provide this suggestion.

Reconsideration and withdrawal of this rejection is requested.

III. Double Patenting

A. *Claims 1-14 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of US Patent No. 6,670,355.*

This rejection is rendered moot in view of the present amendment.

B. *Claim 1, 7, 8, 14 and 22 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 8 and 9 of US Patent No. 6,680,330, in view of Wright et al, cited above, and Mitchell et al, cited above.*

Applicants respectfully traverse this rejection.

The combined teachings of Zhu, Wright and Mitchell fail to suggest the present invention.

The defects in Wright and Mitchell have been previously described. Zhu, Wright and Mitchell are focused on restenosis following injury to vascular wall injury. Zhu relates only to rapamycin dialdehyde. Wright teaches only localized delivery of rapamycin. Mitchell requires heparin, which is not an element of the present claims.

The combined teachings of the prior art do not suggest the ability of rapamycin to prevent lipid accumulation.

Reconsideration and withdrawal of this rejection is requested.

C. *Claims 1, 3, 4, 7, 8, 10, 11, 14, 22, 24 and 25 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 14 of US Patent No. 6,432,973, in view of Wright et al, cited above, and Mitchell et al, cited above.*

The defects in Wright and Mitchell have been previously described. Zhu, Wright and Mitchell are focused on restenosis following injury to vascular wall injury. Zhu relates only to water soluble rapamycin esters having the specified formula. Wright teaches only localized delivery of rapamycin. Mitchell requires heparin, which is not an element of the present claims.

The combined teachings of the prior art fail to suggest the ability of rapamycin to prevent lipid accumulation.

Reconsideration and withdrawal of this rejection is requested.

The Director of the US Patent and Trademark Office is hereby authorized to charge any fee due to Deposit Account 08-3040.

Respectfully submitted,

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